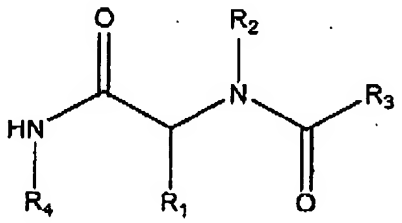
Amendments to the Claims

Please cancel Claims 5, 6 and 18, amend Claims 1, 15, 17, 19 and 20, and add new Claims 21 to 23. The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing

What is Claimed is:

1. (Currently amended) A method of inhibiting rejection of a transplanted organ, tissue or cell in a recipient mammal, the method comprising the step of administering to the recipient mammal an effective amount of ~~an immunosuppressive agent~~ anti-CD40l monoclonal antibody or rapamycin and an effective amount of a compound represented by the following structural formula:



or a physiological salt thereof, wherein:

R_1 is a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted alkyl group;

R_2 is an optionally substituted aralkyl group or an alkyl group substituted with $-NR_5R_6$;

R_3 is a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group;

R_4 a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group; and

R_5 and R_6 are independently selected from a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group or R_5 and R_6 taken together with the nitrogen to which they are attached are a non-aromatic heterocyclic group;

wherein each substituted aryl group, substituted alkyl group or substituted aralkyl group are independently optionally substituted at a carbon atom with -OH, -Br, -Cl, -I, -F, R, $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, -OR, -O-COR, -COR, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, -NHR, $-N(R)_2$, -COOR, -CHO, $-CONH_2$, -CONHR, $-CON(R)_2$, -NHCOR, -NRCOR, $-NHCONH_2$, -NHCONRH, $-NHCON(R)_2$, $-NRCONH_2$, -NRCONRH, $-NRCON(R)_2$, $-C(=NH)-NH_2$, -C(=NH)-NHR, $-C(=NH)-N(R)_2$, $-C(=NR)-NH_2$, -C(=NR)-NHR, $-C(=NR)-N(R)_2$, $-NH-C(=NH)-NH_2$, -NH-C(=NH)-NHR, $-NH-C(=NH)-N(R)_2$, $-NH-C(=NR)-NH_2$, -NH-C(=NR)-NHR, $-NH-C(=NR)-N(R)_2$, $-NRH-C(=NH)-NH_2$, -NR-C(=NH)-NHR, $-NR-C(=NH)-N(R)_2$, $-NR-C(=NR)-NH_2$, -NR-C(=NR)-NHR, -NR-C(=NR)-$N(R)_2$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2NR_2$, -SH, $-SO_kR$ and $-NH-C(=NH)-NH_2$;

wherein each substituted aryl group or substituted aralkyl group are independently optionally substituted at a nitrogen atom with –R', $-N(R')_2$, -C(O)R', $-CO_2R'$, $-C(O)C(O)R'$, $-C(O)CH_2C(O)R'$, $-SO_2R'$, $-SO_2N(R')_2$, $-C(=S)N(R')_2$, $-C(=NH)-N(R')_2$, and $-NR'SO_2R'$;

R' is hydrogen, an alkyl group, phenyl, -O(Ph), $CH_2(Ph)$, heteroaryl or non-aromatic heterocyclic ring;

each R is independently an alkyl, benzyl, or aryl group; or $-N(R)_2$, taken together, can also form a non-aromatic heterocyclic group; and

k is 0, 1 or 2.

2. (Original) The method of Claim 1 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.

3. (Original) The method of Claim 1 wherein the mammal is the recipient of a transplanted stem cell(s).

4. (Original) The method of Claim 1 wherein the transplanted organ, tissue or cell is xenogenic or bio-engineered.

5. (Cancelled)

6. (Cancelled)

7. (Original) The method of Claim 1 wherein R_2 is an optionally substituted heteroaralkyl group or an alkyl group substituted with $-NR_5R_6$.

8. (Original) The method of Claim 7 wherein:

a) R_1 is an optionally substituted aryl group or an optionally substituted C_1-C_4 aralkyl group;

b) R_3 is an optionally substituted aryl group or an optionally substituted C_1-C_4 aralkyl group; and

c) R_4 is an optionally substituted aryl group, an optionally substituted cycloalkyl group, an optionally substituted C_1-C_4 aralkyl group or an optionally substituted C_1-C_4 cycloalkylalkyl group.

9. (Original) The method of Claim 7 wherein:

a) R_1 is an optionally substituted phenyl group or an optionally substituted phenyl-C_1-C_4 alkyl group;

b) R_3 a substituted or unsubstituted phenyl, phenyl-C_1-C_4-alkyl, diphenyl-C_1-C_4-alkyl, pyrazolyl, pyrazolyl-C_1-C_4-alkyl, indolyl, indolyl-C_1-C_4-alkyl, thienylphenyl, thienylphenyl-C_1-C_4-alkyl, furanylphenyl, furanylphenyl-C_1-C_4-alkyl, fluorenyl, fluorenyl-C_1-C_4-alkyl, naphthyl, naphthyl-C_1-C_4-alkyl, quinoxalinyl, quinoxalinyl-C_1-C_4-alkyl, an optionally substituted quinazolinyl, an optionally substituted quinazolinyl-C_1-C_4-alkyl, pyrolyl, pyrolyl-C_1-C_4-alkyl, thienyl, thienyl-C_1-C_4-alkyl, furanyl or furanyl-C_1-C_4-alkyl; and

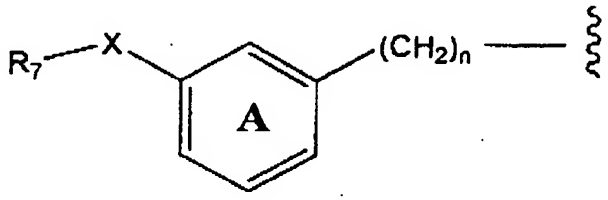
c) R_4 is an optionally substituted phenyl group, an optionally substituted phenyl-C_1-C_4-alkyl group, an optionally substituted diphenyl-C_1-C_4-alkyl group, an optionally substituted C_3-C_8-cycloalkyl-C_1-C_4-alkyl group or an optionally substituted di-(C_3-C_8-cycloalkyl)-C_1-C_4-alkyl group.

10. (Original) The method of Claim 9 wherein R_2 is an optionally substituted imadazolyl-C_1-C_4-alkyl group or a C_1-C_4 alkyl group substituted with $-NR_5R_6$.

11. (Original) The method of Claim 10 wherein:

R_1 is a phenyl group or phenyl-C_1-C_4 alkyl group each optionally substituted with R, $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, -OH, halogen, -OR, -O-COR, -COR, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, -NHR, $-N(R)_2$, -COOR, -CHO, $-CONH_2$, -CONHR, $-CON(R)_2$, -NHCOR, -NRCOR, $-NHCONH_2$, -NHCONRH, $-NHCON(R)_2$, $-NRCONH_2$, -NRCONRH, $-NRCON(R)_2$, $-C(=NH)-NH_2$, -C(=NH)-NHR, $-C(=NH)-N(R)_2$, $-C(=NR)-NH_2$, -C(=NR)-NHR, $-C(=NR)-N(R)_2$, $-NH-C(=NH)-NH_2$, -NH-C(=NH)-NHR, $-NH-C(=NH)-N(R)_2$, $-NH-C(=NR)-NH_2$, -NH-C(=NR)-NHR, $-NH-C(=NR)-N(R)_2$, $-NRH-C(=NH)-NH_2$, -NR-C(=NH)-NHR, $-NR-C(=NH)-N(R)_2$, $-NR-C(=NR)-NH_2$, -NR-C(=NR)-NHR, $-NR-C(=NR)-N(R)_2$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2N(R)_2$, -SH or -SokR;

R_3 is represented by the following structural formula:



R_4 is 2,2-diphenylethyl, 2-phenylethyl, benzyl, diphenylmethyl, 1,2-diphenylethyl, 3,3-diphenylpropyl, benzyl, or 2-pyridylethyl, each optionally substituted with -OH, halogen, R, $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, -OR, -O-COR, -COR, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, -NHR, $-N(R)_2$, -COOR, -CHO, $-CONH_2$, -CONHR, $-CON(R)_2$, -NHCOR, -NRCOR, $-NHCONH_2$, -NHCONRH, $-NHCON(R)_2$, $-NRCONH_2$, -NRCONRH, $-NRCON(R)_2$, $-C(=NH)-NH_2$, -C(=NH)-NHR, $-C(=NH)-N(R)_2$, $-C(=NR)-NH_2$, -C(=NR)-NHR, $-C(=NR)-N(R)_2$, $-NH-C(=NH)-NH_2$, -NH-C(=NH)-NHR, $-NH-C(=NH)-N(R)_2$, $-NH-C(=NR)-NH_2$, -NH-C(=NR)-NHR, $-NH-C(=NR)-N(R)_2$, $-NRH-C(=NH)-NH_2$, -NR-C(=NH)-NHR, $-NR-C(=NH)-N(R)_2$, $-NR-C(=NR)-NH_2$, -NR-C(=NR)-NHR, $-NR-C(=NR)-N(R)_2$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2N(R)_2$, -SH or -SokR;

Ring A substituted or unsubstituted; R_7 is an optionally substituted phenyl, furanyl, thienyl or pyridyl group; n is an integer from 1-4; and X is a bond, CH_2, OCH_2, $CH_2OC(O)$, CO, OC(O), C(O)O, O, S, SO or SO_2;

each R is independently C_1-C_4 alkyl or phenyl optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl; and

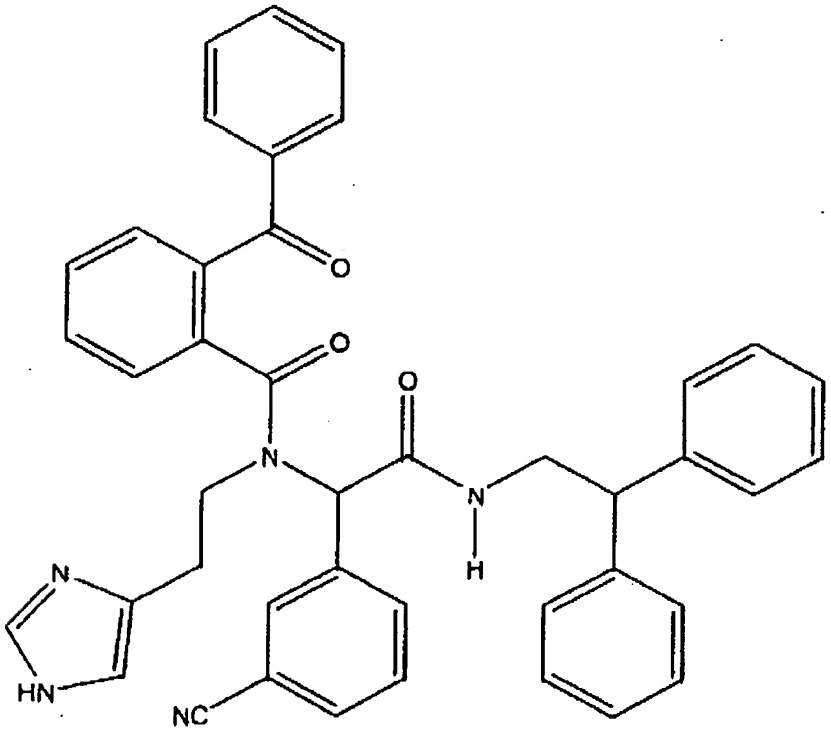
k is zero, one or two.

12. (Original) The method of Claim 11 wherein R_1 is a phenyl group or phenyl-C_1-C_2 alkyl group, each optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, CN, C_1-C_4-alkylthiol, C_1-C_4-haloalkyl or phenoxy; R_4 is 2,2-diphenylethyl, 2-phenylethyl, benzyl, diphenylmethyl, 1,2-diphenylethyl, 3,3-diphenylpropyl, benzyl, or 2-pyridylethyl, each optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, CN, C_1-C_4-alkylthiol, C_1-C_4-haloalkyl or phenoxy; R_7 is an optionally substituted phenyl group; n is 1; and X is CO.

13. (Original) The method of Claim 12 wherein Ring A is unsubstituted and R_7 is a phenyl group optionally substituted with R, -CH_2R, -OCH_2R, -$CH_2OC(O)$R, -OH, halogen, -OR, -O-COR, -COR, -CN, -NO_2, -COOH, -SO_3H, -NH_2, -NHR, -N(R)$_2$, -COOR, -CHO, -$CONH_2$, -CONHR, -CON(R)$_2$, -NHCOR, -NRCOR, -$NHCONH_2$, -NHCONRH, -NHCON(R)$_2$, -$NRCONH_2$, -NRCONRH, -NRCON(R)$_2$, -C(=NH)-NH_2, -C(=NH)-NHR, -C(=NH)-N(R)$_2$, -C(=NR)-NH_2, -C(=NR)-NHR, -C(=NR)-N(R)$_2$, -NH-C(=NH)-NH_2, -NH-C(=NH)-NHR, -NH-C(=NH)-N(R)$_2$, -NH-C(=NR)-NH_2, -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)$_2$, -NRH-C(=NH)-NH_2, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)$_2$, -NR-C(=NR)-NH_2, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)$_2$, -SO_2NH_2, -SO_2NHR, -SO_2N(R)$_2$, -SH or -SO_kR.

14. (Original) The method of Claim 13 wherein R_7 is a phenyl group; and R_2 is 2-(imidazol-4-yl)ethyl.

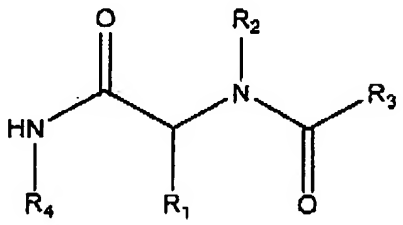
15. (Currently amended) A method of inhibiting rejection of a transplanted organ, tissue or cell in a recipient mammal, the method comprising the step of administering to the recipient mammal an effective amount of [[an]] anti CD40L monoclonal antibody or ~~rapamycin~~ and an effective amount of a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.

16. (Original) The method of Claim 15 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.

17 (Currently amended) A composition comprising ~~an immunosuppressive agent~~ anti-CD40L monoclonal antibody or rapamycin and a compound represented by the following structural formula:



or a physiological salt thereof, wherein:

R_1 is a substituted or unsubstituted aryl group or a substituted or unsubstituted alkyl group;

R_2 is an optionally substituted aralkyl group or an alkyl group substituted with $-NR_5R_6$;

R_3 is a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group;

R_4 a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group; and

R_5 and R_6 are independently selected from a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group or R_5 and R_6 taken together with the nitrogen to which they are attached are a non-aromatic heterocyclic group;

wherein each substituted aryl group or substituted alkyl group are independently optionally substituted at a carbon atom with -OH, -Br, -Cl, -I, -F, R, $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, -OR, -O-COR, -COR, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, -NHR, $-N(R)_2$, -COOR, -CHO, $-CONH_2$, -CONHR, $-CON(R)_2$, -NHCOR, -NRCOR, $-NHCONH_2$, -NHCONRH, $-NHCON(R)_2$, $-NRCONH_2$, -NRCONRH, $-NRCON(R)_2$, $-C(=NH)-NH_2$, $-C(=NH)-NHR$, $-C(=NH)-N(R)_2$, $-C(=NR)-NH_2$, -C(=NR)-NHR, $-C(=NR)-N(R)_2$, $-NH-C(=NH)-NH_2$, -NH-C(=NH)-NHR, $-NH-C(=NH)-N(R)_2$, $-NH-C(=NR)-NH_2$, $-NH-C(=NR)-NHR$, $-NH-C(=NR)-N(R)_2$, $-NRH-C(=NH)-NH_2$, -NR-C(=NH)-NHR, -NR-

$C(=NH)-N(R)_2$, -NR-C(=NR)-NH_2, -NR-C(=NR)-NHR -NR-C(=NR)-$N(R)_2$, -SO_2NH_2, -SO_2NHR, -SO_2NR_2, -SH, -SO_kR and -NH-C(=NH)-NH_2;

wherein each substituted aryl group is optionally independently substituted at a nitrogen atom with –R', -$N(R')_2$, -C(O)R', -CO_2 R', -C(O)C(O)R', -$C(O)CH_2$ C(O)R', -SO_2R', -SO_2 $N(R')_2$, -C(=S)$N(R')_2$, -C(=NH)-$N(R')_2$, and –NR' SO_2R';

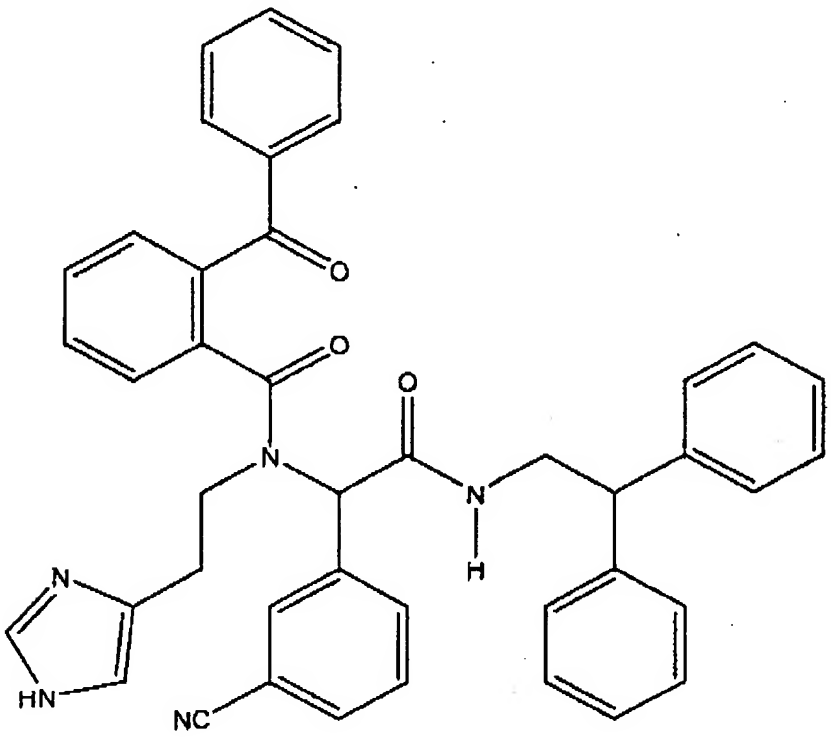
R' is hydrogen, an alkyl group, phenyl, -O(Ph), CH_2(Ph), heteroaryl or non-aromatic heterocyclic ring;

each R is independently an alkyl, benzyl, or aryl group; or -$N(R)_2$, taken together, can also form a non-aromatic heterocyclic group; and

k is 0, 1 or 2.

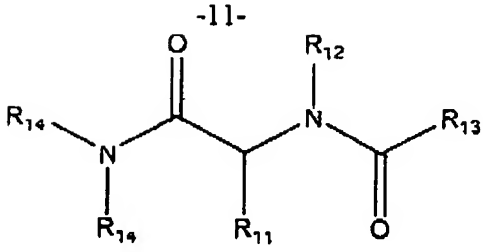
18. (Cancelled)

19. (Currently amended) A composition comprising [[an]] anti CD40L monoclonal antibody ~~or rapamycin~~ and a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.

20. (Currently amended) A method of inhibiting rejection of a transplanted organ, tissue or cell in a recipient mammal, the method comprising the step of administering to the recipient mammal an effective amount of ~~an immunosuppressive agent~~ anti-CD40L monoclonal antibody or rapamycin and an effective amount of a compound represented by the following structural formula:



R_{11} is -H, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heteroaralkyl;

R_{12} is alkyl substituted with $NR_{15}R_{16}$, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaralkyl, or a substituted or unsubstituted heterocycloalkylalkyl;

R_{13} is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted cycloalkylalkyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted benzophenonyl, or a substituted or unsubstituted cycloalkylalkyl; and

each R_{14} is independently, -H, a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heteroaralkyl;

R_{15} and R_{16} are independently selected from H, a substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl or unsubstituted aralkyl or R_{15} and R_{16} together with the nitrogen to which they are attached are a heterocycloalkyl;

wherein each substituted aryl group, substituted alkyl group, substituted heteroaralkyl, substituted heterocycloalkylalkyl, substituted cycloalkylalkyl, substituted benzophenonyl, substituted cycloalkyl, heterocycloalkyl or substituted aralkyl group are independently optionally substituted at a carbon atom with-OH, -Br, -Cl, -I, -F, R, $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, -OR, -O-COR, -COR, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, -NHR, $-N(R)_2$, -COOR, -CHO, $-CONH_2$, -CONHR, $-CON(R)_2$, -NHCOR, -NRCOR, $-NHCONH_2$, -NHCONRH, $-NHCON(R)_2$, $-NRCONH_2$, -NRCONRH, $-NRCON(R)_2$, $-C(=NH)-NH_2$, -C(=NH)-NHR, $-C(=NH)-N(R)_2$, $-C(=NR)-NH_2$, -C(=NR)-NHR,

-C(=NR)-N(R)$_2$, -NH-C(=NH)-NH$_2$, -NH-C(=NH)-NHR, -NH-C(=NH)-N(R)$_2$, -NH-C(=NR)-NH$_2$, -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)$_2$, -NRH-C(=NH)-NH$_2$, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)$_2$, -NR-C(=NR)-NH$_2$, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)$_2$, -SO$_2$NH$_2$, -SO$_2$NHR, -SO$_2$NR$_2$, -SH, -SO$_k$R and -NH-C(=NH)-NH$_2$;

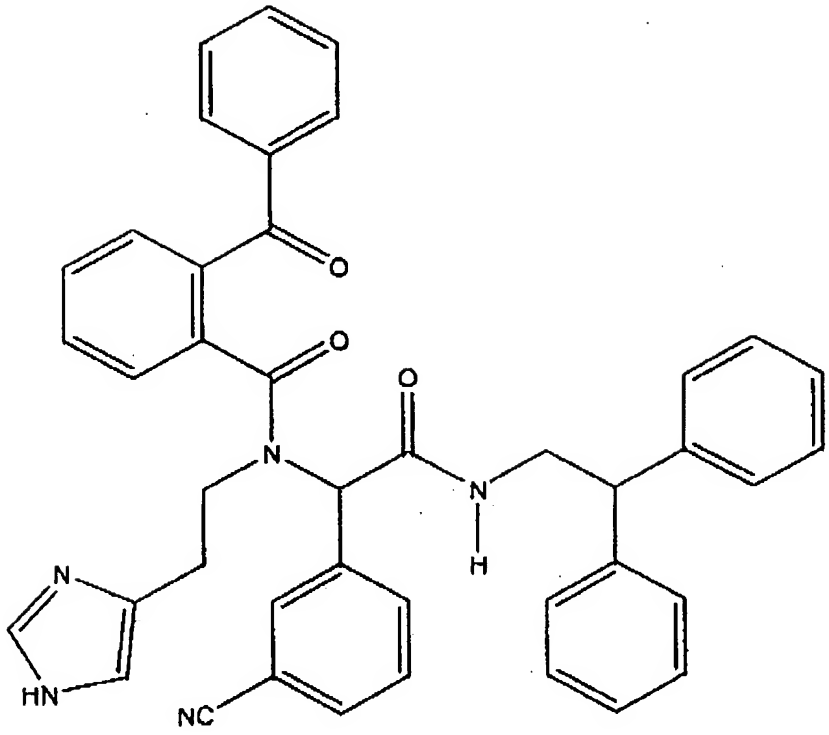
wherein each substituted aryl group, substituted heteroaralkyl, substituted heterocycloalkylalkyl, substituted cycloalkylalkyl,, heterocycloalkyl or substituted aralkyl group are independently optionally substituted at a nitrogen atom with –R', -N(R')$_2$, -C(O)R', -CO$_2$ R', -C(O)C(O)R', -C(O)CH$_2$ C(O)R', -SO$_2$R', -SO$_2$ N(R')$_2$, -C(=S)N(R')$_2$, -C(=NH)-N(R')$_2$, and –NR' SO$_2$R';

R' is hydrogen, an alkyl group, phenyl, -O(Ph), CH$_2$(Ph), heteroaryl or non-aromatic heterocyclic ring;

each R is independently an alkyl, benzyl, or aryl group; or -N(R)$_2$, taken together, can also form a non-aromatic heterocyclic group; and

k is 0, 1 or 2.

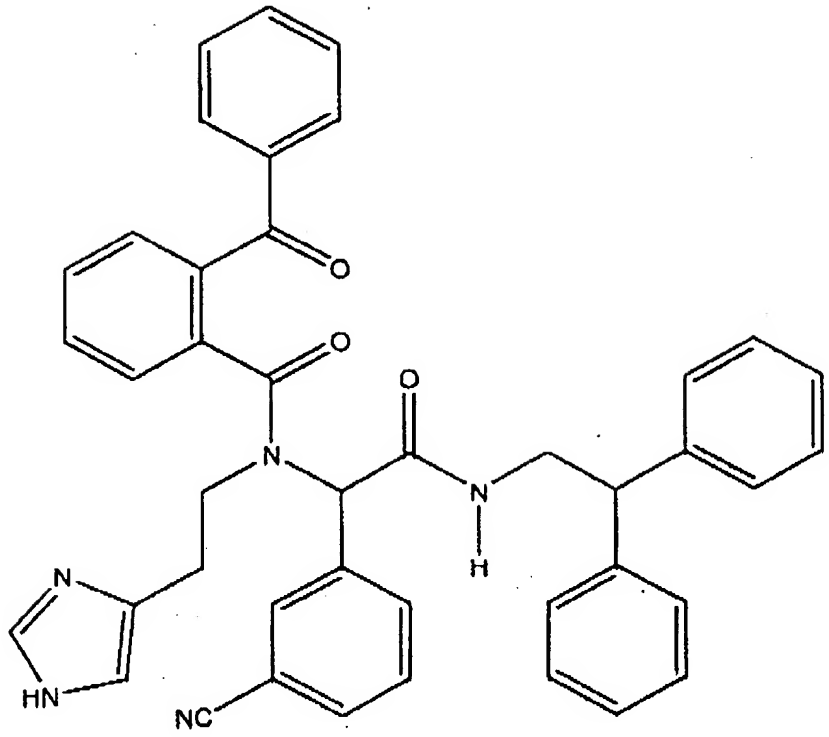
21. (New) A method of inhibiting rejection of a transplanted organ, tissue or cell in a recipient mammal, the method comprising the step of administering to the recipient mammal an effective amount of rapamycin and an effective amount of a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.

22. (New) The method of Claim 21 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.

23. (New) A composition comprising rapamycin and a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.